Patient- and physician-related risk factors for hyperkalaemia in potassium-increasing drug-drug interactions

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Abstract: PURPOSE: Hyperkalaemia due to potassium-increasing drug-drug interactions (DDIs) is a clinically important adverse drug event. The purpose of this study was to identify patient- and physician-related risk factors for the development of hyperkalaemia. METHODS: The risk for adult patients hospitalised in the University Hospital Zurich between 1 December 2009 and 31 December 2011 of developing hyperkalaemia was correlated with patient characteristics, number, type and duration of potassium-increasing DDIs and frequency of serum potassium monitoring. RESULTS: The 76,467 patients included in this study were prescribed 8,413 potentially severe potassium-increasing DDIs. Patient-related characteristics associated with the development of hyperkalaemia were pulmonary allograft [relative risk (RR) 5.1; $p < 0.0001$), impaired renal function (RR 2.7; $p < 0.0001$), diabetes mellitus (RR 1.6; $p = 0.002$) and female gender (RR 1.5; $p = 0.007$). Risk factors associated with medication were number of concurrently administered potassium-increasing drugs (RR 3.3 per additional drug; $p < 0.0001$) and longer duration of the DDI (RR 4.9 for duration 6 days; $p < 0.0001$). Physician-related factors associated with the development of hyperkalaemia were undetermined or elevated serum potassium level before treatment initiation (RR 2.2; $p < 0.001$) and infrequent monitoring of serum potassium during a DDI (interval >48 h: RR 1.6; $p < 0.01$). CONCLUSION: Strategies for reducing the risk of hyperkalaemia during potassium-increasing DDIs should consider both patient- and physician-related risk factors.

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Patient- and Physician-Related Risk Factors for Hyperkalaemia in Potassium-Increasing Drug-Drug Interactions

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Abstract

Purpose

Hyperkalaemia due to potassium-increasing drug-drug interactions (DDIs) is a clinically important adverse drug event. The purpose of this study was to identify patient- and physician-related risk factors for the development of hyperkalaemia.

Methods

The risk for adult patients hospitalised in the University Hospital Zurich of developing hyperkalaemia was correlated with (i) patient characteristics, (ii) number, type and duration of potassium-increasing DDIs, and (iii) the frequency of serum potassium monitoring.

Results

8,413 potentially severe potassium-increasing DDIs were identified in 76,467 patients. (i) Patient-related characteristics associated with development of hyperkalaemia were: pulmonary allograft (RR 5.1; $p < 0.0001$), impaired renal function (relative risk [RR] 2.7; $p < 0.0001$), diabetes mellitus (RR 1.6; $p = 0.002$), and female gender (RR 1.5; $p = 0.007$). (ii) Factors concerning medication were: number of concurrently administered potassium-increasing drugs (RR 3.3 per additional drug; $p < 0.0001$) and longer DDI duration (RR 4.9 for durations ≥ 6 days; $p < 0.0001$). (iii) Physician-related factors associated with development of hyperkalaemia were: undetermined or elevated serum potassium level before starting treatment (RR 2.2; $p < 0.001$) and infrequent monitoring of serum potassium during DDI (intervals > 48 h; RR 1.6; $p < 0.01$).

Conclusion

Strategies for hyperkalaemia risk reduction during potassium-increasing DDIs should consider patient- as well as physician-related risk factors.

Keywords *Drug-drug interactions, Hyperkalaemia, Monitoring, Potassium, risk factors*

Introduction

Although drug-drug interactions (DDIs) are often preventable, they constitute an important cause of adverse drug events leading to increased morbidity and mortality [1-3]. Potassium-increasing DDIs are among the most common DDIs, occurring in up to 10% of hospitalised patients [4,5]. They may induce hyperkalaemia and life-threatening cardiac arrhythmias [6].

It is a challenge for physicians to identify potentially harmful potassium-increasing DDIs due to polypharmacy and the increasing number of therapeutic agents. Computerized physician order entry (CPOE) in combination with clinical

decision support systems (CDSS) may help to detect DDIs and to alert the prescribing physicians. However, they are often based on DDI knowledge bases which do not take patient characteristics into account, resulting in a low specificity of alerts, overalerting and alert fatigue [7-10]. In order to avoid alert fatigue on-demand DDI checks have been implemented into the electronic health record of the University Hospital Zurich [11].

Several studies analysed the risk factors for developing hyperkalaemia during potassium-increasing DDIs, focussing on patient-related risk factors such as demographic parameters and comorbidities and on medication such as number and types of the involved drugs [12-18]. One study considered the effect of potassium monitoring during potassium-increasing DDIs in outpatients [19]. To our knowledge, no study investigated the effect of physician-related risk factors as missing serum potassium measurement at start of therapy and periodicity of serum potassium monitoring during drug therapy in hospitalised patients.

The purpose of this study was to identify patient- and physician-related risk factors for the development of hyperkalaemia. They may provide a foundation for strategies reducing the risk of hyperkalaemia during potassium-increasing DDIs without overalerting.

Methods

Setting

The University Hospital Zurich is a publicly owned, tertiary care academic medical centre with 850 beds and 35,000 hospital admissions per year. We included all inpatients from 01/12/2009 to 31/12/2011 except for patients on dialysis and those hospitalized exclusively in intensive care units.

The local research ethics committee approved the analyses, and patient consent was waived.

Drug-Drug Interactions and Potassium-Increasing Drugs

DDIs were identified using the knowledge base galdat/hospINDEX (distributed by e-mediat AG, Berne, Switzerland – derived from ABDATA Pharma-Daten Service, Werbe- und Vertriebsgesellschaft Deutscher Apotheker, Eschborn, Germany), which tiers DDIs by severity (severity level 1: recommended activity

‘contraindicated’; 2: ‘contraindicated as precaution‘,3: ‘monitoring or adaptation required’, 4: ‘monitoring or adaption in case of risk factors’, 5: ‘monitoring as a precaution’, 6: ‘no activity required’) [20]. DDIs with severity levels 1 to 3 were considered as severe.

Potassium-increasing drugs (PIDs) were defined as drugs involved in severe potassium-increasing DDIs according to the knowledge base galdat/hospINDEX. Thus, PIDs included angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin antagonists (angiotensin-receptor blockers), direct renin inhibitors, immunosuppressive agents (calcineurin inhibitors), potassium-sparing diuretics (aldosterone-receptor antagonists and epithelial sodium channel blockers), potassium supplements, and trimethoprim (ingredient of cotrimoxazole), irrespective of whether these drugs were ordered as a monotherapy or participated in a DDI.

Serum Potassium Measurements

Serum potassium levels were categorized into 4 groups: (i) hypokalaemia: serum potassium ≤ 3.2 mEq/l [21]; (ii) reference range: ≥ 3.3 mEq/l to ≤ 4.5 mEq/l [22]; (iii) moderately increased: ≥ 4.6 mEq/l to ≤ 5.4 mEq/l; and (iv) hyperkalaemia: ≥ 5.5 mEq/l [12].

The following parameters, explored for their association with hyperkalaemia, need to be defined:

(i) estimated glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault equation [23] with the first serum creatinine level measured during DDI ± 1 day. The kidney dysfunction categories ‘normal’, ‘mild’, and ‘moderate to severe’ were assigned to GFR ≥ 90 ml/min, 60 ml/min ≤ GFR < 90 ml/min, and GFR < 60 ml/min, respectively [24].

(ii) Blood transfusions were identified by ICD-9 (International Classification of Diseases, World Health Organization, Geneva, Switzerland) treatment code 99.0.

(iii) Comorbidities were identified using ICD-10 discharge diagnosis codes E10, E11, E12, E13, and E14 for diabetes mellitus, code I10 for arterial hypertension, code I50 for heart failure, codes I50.11 and I50.12 for NYHA class I/II, codes I50.13 and I50.14 for NYHA class III/IV, and code Z94.2 for pulmonary allograft.

Statistical Analyses

Data analyses and statistical tests were performed using the R language and environment for statistical computing, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). P levels of ≤ 0.05 were considered statistically significant. The two-tailed chi-square test was used to analyse categorical data of 2x2 contingency tables. P levels for multiple comparisons were adjusted using Holm correction [25]. Binomial confidence intervals were calculated using the Clopper-Pearson method [26].

Results

We analysed data of 76,467 inpatients. Mean duration of hospitalisation for all patients was 6.9 days, and 13.5 days for patients with potassium-increasing DDIs. Patients' characteristics are listed in Online Resource 1.

A total of 1,543,578 drugs were prescribed, resulting in 20.1 drugs per patient on average. PIDs accounted for 5.0% of all drug prescriptions. Potassium supplements were the most frequently ordered PIDs (30% of all PID prescriptions), followed by immunosuppressive agents (21%), ACE inhibitors (20%), angiotensin antagonists (14%), trimethoprim (9%), potassium-sparing diuretics (6%), and direct renin inhibitors (0.3%).

Drug-Drug Interactions

The knowledge base identified 197,351 potential DDIs (2.6 per patient), of which 90,811 were classified severe (1.2 per patient). The 8,413 potassium-increasing DDIs constituted the largest part of level-1 DDIs (972 out of 1'402 DDIs) and also played an important role in level-3 DDIs (7'441 out of 84'093 DDIs).

17% of the potassium-increasing DDIs were started lacking a serum potassium measurement within the preceding 48 hours. Moreover, 60 potassium-increasing DDIs (0.7%) were ordered despite the presence of hyperkalaemia. The histogram of the last serum potassium levels measured within 48 hours prior to a potassium-increasing DDI showed a bimodal distribution (Fig. 1), with one peak in the hypokalaemic range and another one in the reference range. Most of the therapies that were started in the hypokalaemic range included a potassium supplement, suggesting that they were deliberately prescribed to correct the low potassium.

The frequency of daily serum potassium level measurements decreased from 72% on the day before DDI to 59% on the first day of DDI and remained between 46% and 53% during the next two weeks (the frequencies per day are shown in Online Resource 2).

The intervals between serum level measurements during potassium-increasing DDIs present a wide range (median interval 24 hours) with 84.8% of the serum level measurements embedded in intervals ≤ 48 hours. Thus, 15.2% of the monitoring intervals exceeded 48 hours (the frequency distribution of serum potassium monitoring intervals is presented in Online Resource 3). Similar monitoring frequencies were observed in surgical and non-surgical specialties. The median monitoring period was 1.0 days in both groups. In surgical specialties the monitoring intervals exceeded 48 and 96 hours in 14.3% and 2.3%, respectively. In non-surgical specialties the respective numbers were 15.6% and 2.5%.

Hyperkalaemia

The occurrences of hyperkalaemia were analysed after the exclusion of DDIs started in the presence of hyperkalaemia (60 DDIs in 28 patients), leaving 8,353 potassium-increasing DDIs in 5,609 patients for further analysis: Hyperkalaemia was observed during 161 DDIs concerning 78 patients. A further increased serum potassium level of > 6.0 mEq/l occurred during 31 DDIs observed in 15 patients. The consideration of the initial serum potassium level and of the serum potassium monitoring frequency were two physician-related risk factors for hyperkalaemia: (i) Starting a potassium-increasing DDI with either an undetermined or an elevated (> 4.5 mEq/l) serum potassium level (2,252 DDIs, 71 with hyperkalaemia during DDI) was associated with an increased relative risk (RR) of 2.2 of developing a hyperkalaemia, compared to starting a DDI at normokalaemic or hypokalaemic levels (6,101 DDIs, 90 with hyperkalaemia during DDI; chi-square test: $p < 0.001$). (ii) Monitoring intervals exceeding 48 hours during the interaction period were associated with a higher risk of hyperkalaemia: A new hyperkalaemia was detected in 1.00% (36 out of 3'635) of the serum potassium levels measured more than 48 hours after the preceding measurement, compared to 0.61% (122 out of 20'092) when levels were measured within 48 (chi-square

test: $p < 0.01$).Three factors regarding medication were associated with development of hyperkalaemia:

(i) The more PIDs were concurrently administered, the higher was the risk for hyperkalaemia (Table 1): Starting with a RR of 1 for patients without PIDs, the RR increased to 3.9 for PID monotherapies (chi-square test: $p < 0.001$) and 5.7 for therapies with two concurrent PIDs ($p = 0.040$), peaking at 18.1 for three or more concurrent PIDs ($p < 0.001$). The triple PID combination of immunosuppressive agents plus trimethoprim plus ACE inhibitor achieved the highest RR of 29. Nevertheless, the absolute risk was low, with hyperkalaemia occurrences of 0.7%, 1.0 and 3.3% for patients treated with one, with two and with more than two PIDs, respectively.

(ii) The duration of potassium-increasing DDIs was significantly associated with hyperkalaemia.

(iii) A high number of concurrently administered potassium-decreasing drugs were associated with higher risk of hyperkalaemia. Blood transfusions showed a non-significant trend towards an increased risk of hyperkalaemia.

Five out of seven electronically available patient-related characteristics predicted the development of hyperkalaemia in a univariate analysis (Table 2): (i) female gender, (ii) renal impairment, (iii) diabetes mellitus, (iv) pulmonary allograft, and (v) serum potassium level exceeding the normokalaemic range before onset of potassium-increasing DDI.

The effect of renal impairment on the risk of hyperkalaemia was analysed in greater detail as a function of the number of concurrently administered PIDs (Fig. 2). The risk significantly increased for patients with moderate to severe kidney impairment compared to patients with mild kidney impairment. Hyperkalaemia observed during potassium-increasing DDIs was associated with a significantly increased risk of transfer to the intensive care unit (ICU) or death (Table 3). The risk of death within 2 days after detecting hyperkalaemia was 5.3 times higher than for non-hyperkalaemic patients also treated with concurrent PIDs. The likelihood of being transferred to the ICU was 1.9 times higher for hyperkalaemic patients. Furthermore, the length of hospitalisation increased significantly for patients with hyperkalaemia during potassium-increasing DDIs.

Discussion

A number of patient- and physician-related factors have been analysed in order to identify characteristics associated with development of hyperkalaemia during potassium-increasing DDIs.

The study demonstrates that physician-related factors affect the risk for developing hyperkalaemia in hospitalised patients: (i) Less frequent monitoring of serum potassium during DDI was associated with an increased risk of hyperkalaemia. Rapid development of hyperkalaemia may be missed with longer monitoring intervals [27] and subsequent therapy adjustments may be delayed. The frequency of serum potassium level measurements decreased after the first day of DDI (as shown in Online Resource 2), despite the finding that the risk of hyperkalaemia increased with a longer DDI duration (Table 2). (ii) Furthermore, lack of serum level monitoring at onset of potassium-increasing DDIs correlated with an increased risk for developing hyperkalaemia (Table 2). Previously such an association has been reported for outpatients [19].

Medication also affected the risk for hyperkalaemia: (i) As expected, the risk for hyperkalaemia increased with the number of concurrently administered PIDs. (ii) Surprisingly, the risk of hyperkalaemia also rose with a growing number of concurrent potassium-decreasing drugs. A possible explanation for this finding might be that potassium-decreasing drugs were used to correct higher serum potassium levels. (iii) The level of severity of the involved DDIs was not predictive for the likelihood of developing hyperkalaemia. This might be due to the frequent usage of the contraindicated level-1 potassium-increasing DDI (i.e. the combination of potassium-sparing diuretics with potassium supplements) to correct a hypokalaemia (Fig. 1) [10] including a high degree of physician awareness [28]. The agreement whether these DDIs should indeed be labelled contraindicated is low [29,30].

Finally, our study confirmed patient-related characteristics known to be associated with development of hyperkalaemia: (i) moderately or severely impaired renal function (Fig. 2); (ii) diabetes mellitus [6,31]; (iii) the highest risk concerned pulmonary allograft, mainly due to PID combinations of immunosuppressive agents, trimethoprim, and ACE inhibitor [32,33]; (iv) female gender, confirming another analysis of gender as a predictor in drug-induced hyperkalaemia [34]; (v) elevated serum potassium (> 4.5 mEq/l) at onset of the DDI.

In contrast to other studies, we couldn't establish an association between hyperkalaemia during potassium-increasing DDIs and age or hospitalisation in surgical versus non-surgical specialties [12].

There are limitations to our analysis: Dosing of PID prescriptions were not considered. Only DDIs between two specific drugs were explored. PIDs not listed in the DDI knowledge base, e.g. nonsteroidal anti-inflammatory drugs or heparin, were not taken into account.

The association between the presence of hyperkalaemia during potassium-increasing DDIs and transfer to the ICU or death within two days was considered statistically significant. However, the positive correlation does not imply causation, since the relationship is influenced by comorbidities and therapies.

Overall, the risk of developing hyperkalaemia was low, occurring only in one out of fifty potassium-increasing DDIs. This is in line with other reports [28].

Despite infrequent occurrences, hyperkalaemias must be detected in order to avoid severe complications. Clinical decision support systems may help the prescribing physicians to adjust the therapy early. However, unspecific alerts will lead to alert fatigue [7-9]. The present study improves the understanding of factors associated with hyperkalaemia [12] and adds physician-related factors, which may help to design more specific alerts.

Conclusions

Strategies for prevention of hyperkalaemia during treatment with potassium-increasing drugs should consider patient- as well as physician-related characteristics:

Impaired renal function, diabetes mellitus, and pulmonary allograft are important patient-related characteristics. A higher number of concurrently administered PIDs and a longer DDI duration are risk factors concerning medication.

Physician-related factors include undetermined or elevated serum potassium levels before starting treatment and inadequate frequency of potassium monitoring during DDIs. Therefore, measuring serum potassium levels systematically before prescribing therapies inducing potassium-increasing interactions and periodic monitoring are essential for reducing the risk of hyperkalaemia.

Contributions of Authors statement

E. Eschmann designed and performed the research, analysed and interpreted data, and wrote the manuscript.

P. Beeler, V. Kaplan, M. Schneemann, and G. Zünd contributed to the research, interpreted data, and edited the manuscript.

J. Blaser designed the research, interpreted data, and edited the manuscript.

All authors approved the manuscript.

Disclosure of Conflict of Interests

The authors declare that they have no conflict of interest.

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Artwork

Figure Captions

Fig. 1 Last serum potassium level measured within 48h prior to potassium-increasing DDIs with and without potassium supplements

Fig. 2 Occurrences of hyperkalaemia as a function of the number of concurrently administered PIDs categorized by the estimated GFR[1]

Graphics program used to create the artwork

Fig. 1: R language and environment for statistical computing, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria)

Fig. 2: MS Word 2010 with an embedded R graphic

Caption of electronic supplementary material

Online Resource 1: patients' characteristics

Online Resource 2: Monitoring of serum potassium

Online Resource 3: Serum potassium monitoring intervals during potassium-increasing DDIs

[1] Inclusion and exclusion criteria base on those of Table 1, whereby only patients including GFR estimation were considered. Dots represent the mean; lines encompass a 95% confidence interval.

Table 1 Occurrences of hyperkalaemia as a function of ...
Click here to download Table: PatientPhysicianRelatedRF_in_PotassiumIncDDIs rev02 Table1.docx

Table 1 Occurrences of hyperkalaemia as a function of concurrent administration of PIDs

therapy			**hyperkalaemia**	
No. of concurrent PID administrations	**PIDs involved**	**total No. of patients[a]**	**No. of patients**	**per total**
no PID administration	total	30,723	56	0.2 %
PID monotherapy[b]	total	17,010	122	0.7 %
concurrent administration of 2 PIDs	total[c]	4,221	44	1.0 %
including	ACE inhibitor or angiotensin antagonist plus potassium supplement	2,311	24	1.0 %
	ACE inhibitor or angiotensin antagonist plus potassium-sparing diuretic	824	9	1.1 %
	Trimethoprim[d] plus PID	418	3	0.7 %
	potassium-sparing diuretic plus potassium supplement[d]	380	6	1.6 %
	Immunosuppressive agent plus PID	353	2	0.6%
concurrent administration of 3 or more PIDs	total	1’028	34	3.3 %
including[e]	ACE inhibitor or angiotensin antagonist plus potassium-sparing diuretic plus potassium supplement	380	10	2.6 %
	Immunosuppressive agent plus trimethoprim[d] plus PID	359	19	5.3 %

ACE inhibitor or angiotensin antagonist plus potassium supplement plus trimethoprim[c]	245	2	0.8 %

[a] Patients with at least one serum potassium level measurement within 48h prior to onset of therapy, the last value not being hyperkalaemic (no time restriction for patients with no PID administration).

[b] involved PIDs (in decreasing order of monotherapy leading to hyperkalaemia): potassium supplements, trimethoprim, immunosuppressive agents (calcineurin inhibitors), ACE inhibitors, angiotensin antagonists, potassium-sparing diuretics, and direct renin inhibitors.

[c] total of patients exposed < sum of patients exposed, as the same patient might have been considered for two different potassium-increasing DDI groups, if they were not overlapping.

[d] trimethoprim is part of the combination antibiotic cotrimoxazole (sulfomethoxazole and trimethoprim) used as therapy or prophylaxis for certain infections.

[e] concurrent DDIs with less than 100 patient exposed were not considered.

Table 2 Development of hyperkalaemia during potassium-increasing DDIs as a function of selected parameters

Group	Characteristic	Property	Total No. of potassium-increasing DDIs	No. of potassium-increasing DDIs with hyperkalaemia	Percentage of DDIs with hyperkalaemia [%]	Relative risk (95% CI)	Chi-square test
Overall			8'353	161	1.9		
Demographics	Age (rounded quartiles)	< 57y	2'147	54	2.5	1.00	0.0984
		≥ 57y, < 66y	2'076	32	1.5	0.62 (0.40-0.95)	
		≥ 66y, < 75y	1'983	39	2.0	0.79 (0.52-1.19)	
		≥ 75y	2'147	36	1.7	0.67 (0.44-1.02)	
	Gender	male	5'041	80	1.6	1.00	0.0067*
		female	3'312	81	2.5	1.53 (1.13-2.07)	
Therapy	Severity level of potassium-increasing DDI[a]	1	968	20	2.1	1.00	0.8341
		3	7'385	141	1.9	0.92 (0.58–1.47)	
	Duration of potassium-increasing DDI (rounded quartiles)	< 1d	1'938	14	0.7	1.00	< 0.0001*
		≥ 1d, <3d	2'506	29	1.2	1.60 (0.85-3.01)	
		≥ 3d, <6d	1'856	46	2.5	3.37 (1.86-6.11)	
		≥ 6d	2'053	72	3.5	4.72 (2.67-8.35)	

	Number of concurrent potassium-decreasing drugs[b]	0	2'092	38	1.8	1.00	0.0027*
		1	4'150	64	1.5	0.85 (0.57-1.27)	
		≥ 2	2'111	59	2.8	1.52 (1.02-2.28)	
	Recent blood transfusion[c]	no	8'000	148	1.9	1.00	0.0243
		yes	353	13	3.7	1.96 (1.12-3.41)	
Comorbidities	Renal function (estimated GFR)	≥ 90 ml/min	2'429	29	1.2	1.00	< 0.0001*
		≥ 60 to < 90 ml/min	2'313	38	1.6	1.37 (0.85-2.21)	
		< 60 ml/min	2'727	87	3.2	2.62 (1.73-3.98)	
		Unknown[d]	884	7	0.8	0.67 (0.29-1.51)	
	Diabetes mellitus	no	6’231	103	1.7	1.00	0.0024*
		yes	2’122	58	2.7	1.64 (1.19-2.25)	
	Primary arterial hypertension	no	3'855	71	1.8	1.00	0.6545
		yes	4'498	90	2.0	1.08 (0.80-1.48)	
	lung transplant	no	7'757	116	1.5	1.00	< 0.0001*
		yes	596	45	7.6	4.76 (3.41-6.66)	
Progression	Last serum potassium before	hypokalaemic	1'390	21	1.5	1.03 (0.63-1.67)	< 0.0001*

parameters	onset of DDI[e]	normokalaemic	4'711	69	1.5	1.00	
		> 4.5 mEq/l	815	36	4.4	2.93 (1.97-4.36)	
		Unknown[d]	1'437	35	2.4	1.65 (1.10-2.46)	
Department		surgical specialties	3'408	63	1.8	1.00	0.7232
		non-surgical specialties	4'945	98	2.0	1.07 (0.78-1.46)	

[a] coadministration of potassium-sparing diuretics plus potassium supplements is the only severity level 1 ("contraindicated") potassium-increasing DDI listed in the used knowledge base. All other potassium-increasing DDIs included in this study are classified as severity level 3 DDI ("monitoring or adaptation required")

[b] prescriptions of kaliuretic diuretics coexisting at onset of potassium-increasing DDIs

[c] administered between the day prior to DDI and the end of DDI

[d] not considered in chi-square test

[e] maximum of 48h before onset of DDI

* significant using Holm correction for multiple testing (with $\alpha = 0.05$, $n = 12$)

Table 3 Correlation of death, transfer to ICU and length of stay with the presence and absence of hyperkalaemia during potassium-increasing DDIs

	patients with hyperkalaemia during potassium-increasing DDIs	**patients without hyperkalaemia during potassium-increasing DDIs**
death *[1]	5/103 (4.9%) [a]	50/5,506 (0.9%) [b]
transfer to ICU *[1]	9/103 (8.7%) [a]	245/5,506 (4.5%) [b]
length of hospitalisation *[2]	26.8 ± 26.5d [c]	12.2 ± 13.8d [c]

*[1] significant increase (chi-square test: $p < 0.05$)

*[2] significant increase (Mann-Whitney test: $p < 0.001$)

[a] death respectively transfer to ICU within 2 days of occurrence of hyperkalaemia

[b] death respectively transfer to ICU during or less than 2 days after potassium-increasing DDI

[c] days; mean ± standard deviation

Fig. 1 Last serum potassium level measured within ...

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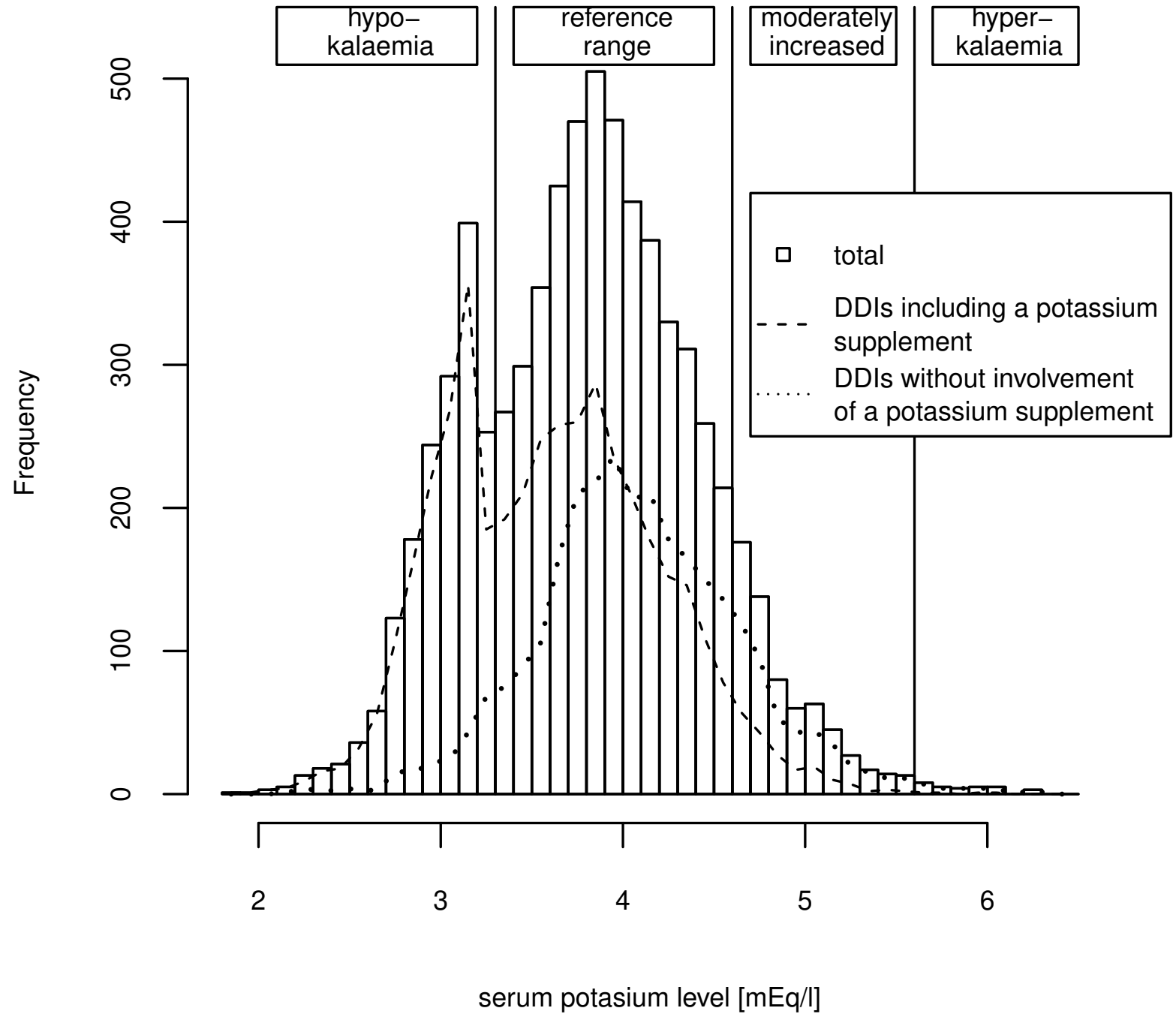

Fig. 2 Occurrences of hyperkalaemia as a function of ...

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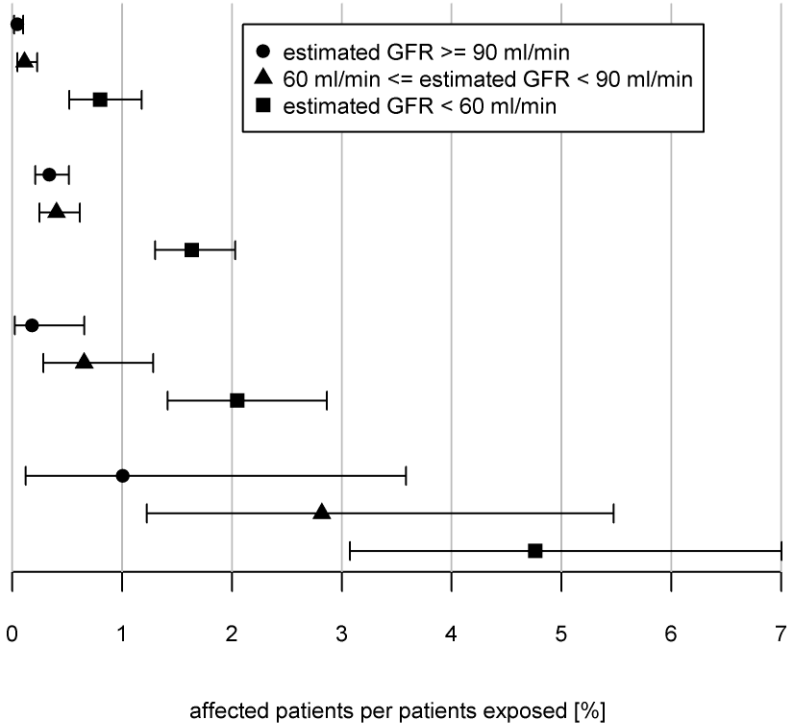
No. of concurrent PID administrations	% developing hyperkalaemia
no PIDs	0.04 %
	0.11 %
	0.80 %
potassium-increasing monotherapy	0.34 %
	0.40 %
	1.60 %
2 concurrent PIDs	0.18 %
	0.65 %
	2.00 %
≥3 concurrent PIDs	1.00 %
	2.80 %
	4.80 %



Online Resource 1 Patients' characteristics

	all patients	**patients with potassium-increasing DDI**	**patients without any hyperkalaemia during potassium-increasing DDI**	**patients with hyperkalaemia during potassium-increasing DDI**
age[a]	49.6 ± 23.2y	65.8 ± 13.8y	65.8 ± 13.8y	65.5 ± 15.7y
gender (females)	50.3%	31.3%	31.0%	45.6%
comorbities associated with hyperkalaemia				
impaired renal function[b]	13.0%	32.5%	32.0%	58.3%
diabetes mellitus	9.3%	24.7%	24.6%	35.0%
arterial hypertension	21.8%	54.8%	54.9%	52.4%
pulmonary allograft	1.1%	4.1%	3.9%	19.4%
heart failure	4.3%	20.9%	20.7%	31.1%
NYHA class I/II[c]	1.0%	4.2%	4.2%	4.9%
NYHA class III/IV[c]	2.2%	11.6%	11.5%	17.5%

[a] mean ± standard deviation

[b] estimated glomerular filtration rate < 60 ml/min

From: Patient- and Physician-Related Risk Factors for Hyperkalaemia in Potassium-Increasing Drug-Drug Interactions. European Journal of Clinical Pharmacology.

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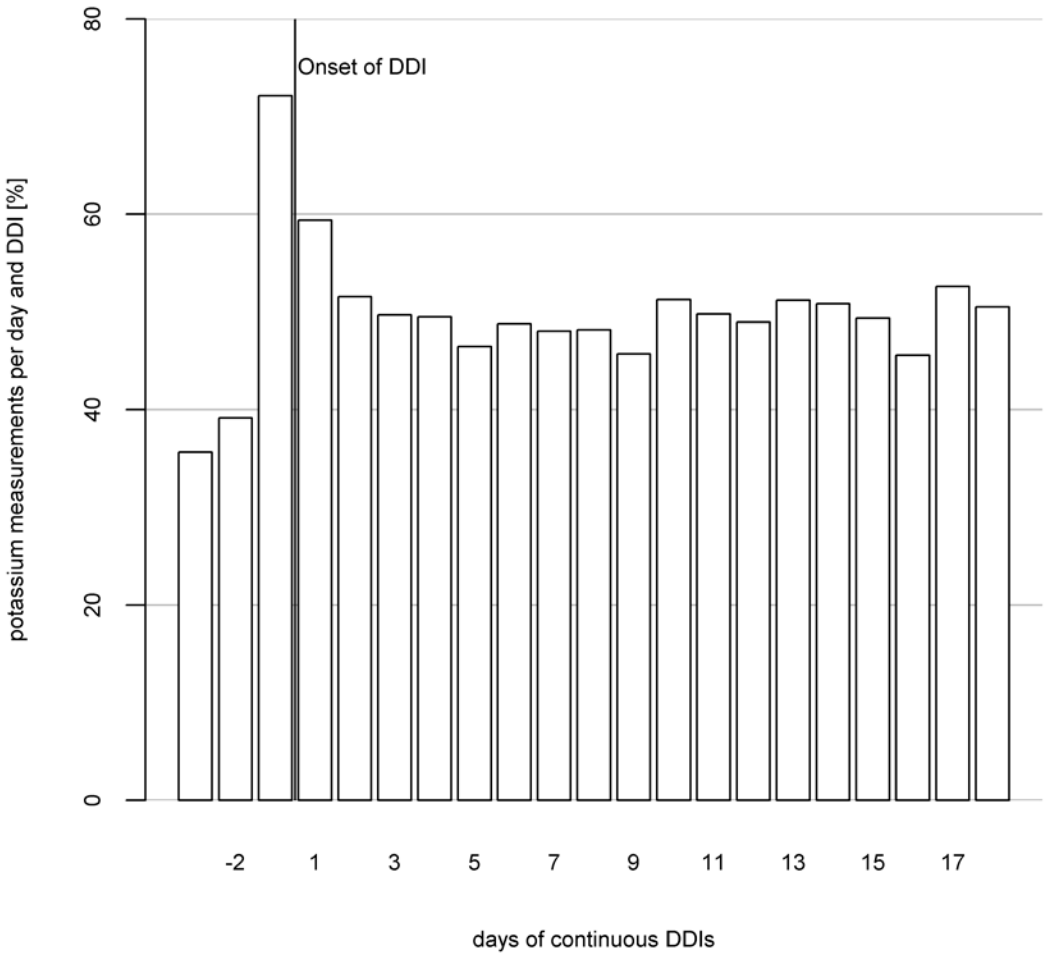
Online Resource 2 Monitoring of serum potassium



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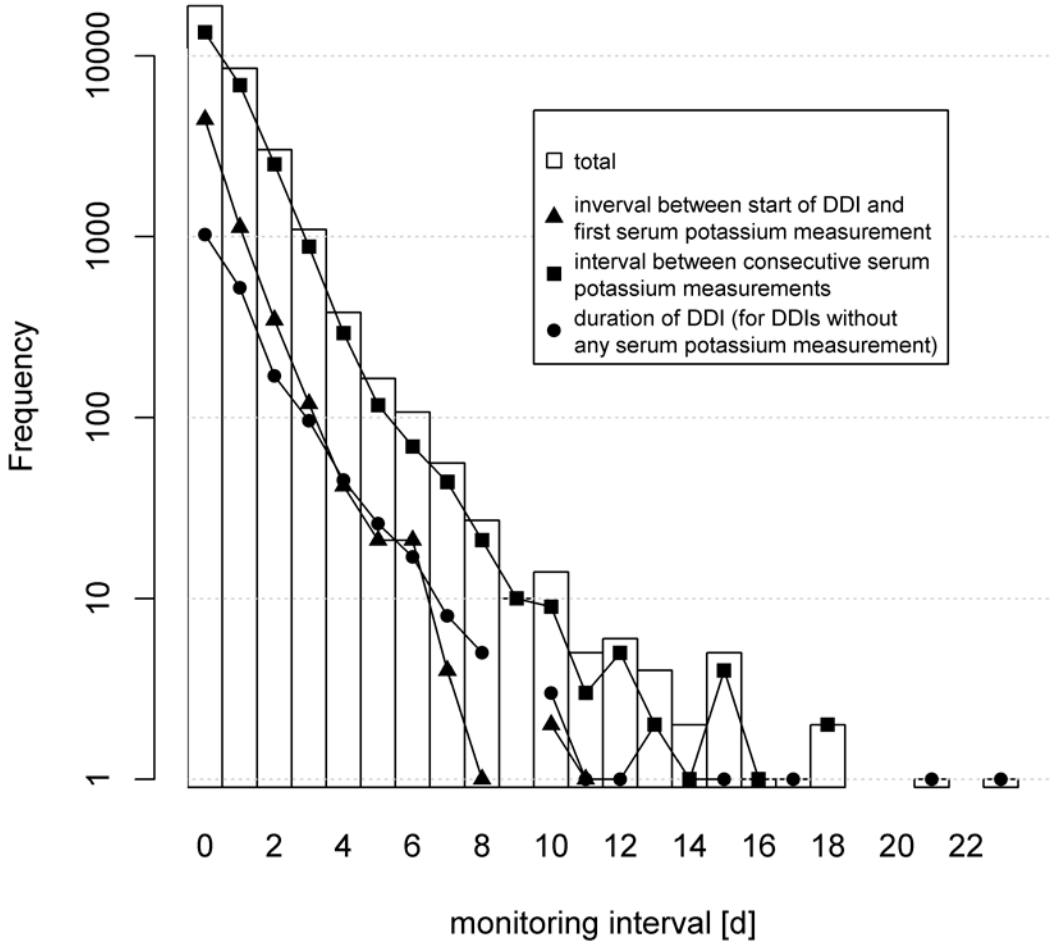
Online Resource 3 Serum potassium monitoring intervals during potassium-increasing DDIs



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